Nightmares and Mirtazapine—Time to Be Vigilant

Sir,

Mirtazapine, an antidepressant drug, is an atypical group of medication. By blockade of central α2-adrenergic auto and heteroreceptors, it promotes serotonergic and noradrenergic transmission. It is also called "noradrenergic and specific serotonergic antidepressant" (NaSSA). It is often highlighted as the best, fulfilling the needs for tolerability and safety in overdose. Its pharmacological properties such as improvement in sleep and reduction of anxiety have made it popular in treating and managing patients who have anxiety or depression along with insomnia.[1,2]

A 48-year-old male presented with complaints of sleep disturbances and lack of interest in sexual activities for three months. He had difficulty in the initiation and maintenance of sleep. He also added that he experienced anxiety on and off, and his functioning in all work-related activities had been affected adversely to a significant extent in the last few months. He had a history of ischemic heart disease a few months before for which he was being treated with metoprolol 25 mg, atorvastatin 10 mg, and clopidogrel 75 mg. But since then he developed anxiety, mood swings (being low most of the time), sleep disturbances (difficulty in initiation and maintenance), and health-related worries (e.g., "something wrong is going to happen to me"). He suffered from these thoughts for these few months (3 months). After that, he consulted us for further evaluation.

All clinical examinations pertaining to all systems were normal. There was increased psychomotor activity. Mood was subjectively fearful and objectively anxious and sad. He was preoccupied with anxious ruminations about health and ideas of hopelessness. There was no history of concomitant use of any other drugs, including herbal medicines or alcohol. All the routine blood investigations done were within the normal range.

With the mentioned history and as per ICD 10 criteria, the patient was diagnosed as a case of moderate depressive episode. The patient was prescribed T. mirtazapine 7.5 mg at night for two days and asked to take 15 mg from the third day onwards. Within three days, the patient again reported with complaints of sudden awakening with profuse sweating in the middle of the night. He was getting terrific dreams of "some unknown person coming to kill me" and had total insomnia. He could recollect the entire dream and had described the episode to his wife. He was advised to stop mirtazapine immediately and was started on tablets sertraline 50 mg and clonazepam 0.5 mg, both at night. The patient reported having no nightmares from the fourth day, with good sleep. During his subsequent visits and follow up, there were no other complaints, and the patient is being currently treated with sertraline and clonazepam along with his cardiac drugs.

This case shows the temporal relationship between the initiation of treatment with mirtazapine and the onset of nightmares and their disappearance with discontinuation of the drug. Mirtazapineinduced nightmares have been reported previously[3-6] (**Table 1**). Among those three published reports mentioned in the table, two cases are from India and one from Philadelphia. Among the two Indian cases, one was initially managed with escitalopram, followed by 7.5 mg of mirtazapine.[6] But the other two cases were directly managed with mirtazapine at 15 mg OD. Our case report adds to this list of the existing three reports, extending the adverse event signals of mirtazapine-induced nightmares. The uniqueness of our case, as mentioned above, is that nightmares developed at a low starting dose of mirtazapine, while in the other published cases where 7.5 mg mirtazapine induced nightmares, the patients had nightmares when they were shifted from escitalopram to miratazapine. In our patient, the plausible cause of nightmares may be mirtazapine because of the temporal relationship. According to the Naranjo scale, it is considered as "possible-score of 2." The case has been reported timely to the Pharmacovigilance Program of India (PvPI). The pharmacology and the possible molecular mechanism[6] has been previously proposed in various cases. In depressed patients, the sleep architecture is disturbed, and it is noticed that the latency of rapid eye movement (REM) sleep gets shortened and REM sleep time prolonged. Even after a single dose, in some sensitive patients, mirtazapine has shown good enhancement in their sleep quality.[7] Mirtazapine decreases sleep latency, improves sleep quality, and increases slow-wave sleep.[8] Sleep disorders are considered extremely rare adverse events with mirtazapine. Most of the antidepressants suppress REM sleep,[3] causing insomnia.

We also looked into the other possibility that this adverse reaction is caused by any of the co-administered drugs. We found reports on atorvastatin and metoprolol causing nightmares.[9,10] We ruled out the possibility because the patient responded on dechallenging by mirtazapine during which he was still on cardiovascular drugs; he is presently continuing the cardiovascular drugs without any episodes of nightmares. From the available reports, it is inferred that we should be vigilant about nightmares even with low doses of mirtazapine.

Declaration of Conflicting Interests
The authors declare that there are no conflicts of interests regarding this study.

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TABLE 1.
Published Literature on Nightmares by Mirtazapine

Citation	Clinical Condition	Age/Sex	Country	Drug/Dose	Inference	Rescue Medication
Mathews et al.	Depressive symptoms	52/ M	Philadelphia	Mirtazapine 15 mg OD	Nightmares	Not Mentioned
Dang et al.	Depressive symptoms	21/ M	Goa, India	Mirtazapine 15 mg OD	Nightmares	Drug stopped. Treated with Fluoxetine
Menon et al.	Major depression	21/ F	Puducherry, India	Mirtazapine 7.5 mg OD	Nightmares	Sertraline 50 mg

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Management of Post-Liver-Transplant Delirium with Melatonin: A Case Report

Melatonin is known to play a key role in managing multiple bodily functions such as controlling the chronobiologic cycle of the body and resetting the circadian rhythm. It also acts as an antioxidant at the intracellular level, has strong anti-apoptotic activity, has anti-inflammatory and analgesic properties, helps in adaptation to the environmental and neuroendocrine system, and delays the progression of various hormone-dependent malignancies. It also plays a role in immune regulation, neuroprotection, and sleep regulation.[1]

Given its role in the chronobiological cycle, melatonin has been evaluated for the prevention and management of delirium.[2] The antioxidant properties of melatonin have been utilized for preventing and managing a range of liver injuries and diseases[3,4] and the prevention of medication-associated nephrotoxicity.[5] Given its potent antioxidant properties, it has also been used in organ transplant patients to prevent graft rejection. It has been evaluated in liver transplant patients as part of a multidrug pre-transplant pharmacological cocktail.[6]

Delirium is one of the acute complications of a liver transplant, with a reported incidence of 21%, and is associated with prolonged hospital stay, longer intensive care unit stay, and higher six months mortality.[7] Accordingly, effective management of delirium in patients undergoing liver transplantation is of paramount importance. Considering the antioxidant, anti-inflammatory, and beneficial effects of melatonin, with no associated cardiac complications, it can be considered as a promising agent for the management of delirium in patients undergoing a liver transplant. However, no studies have evaluated the role of melatonin in the management of